EXHIBIT A

this sounded very intriguing.

Number two, she didn't know this, but we had actually just finished a study looking at nicotinic receptors in the brains of individuals that died with Alzheimer's disease, with Peter Whitehouse. And what we found, that unlike muscarinic receptors, which appeared to be spared, there was substantial losses in nicotinic receptors in the cortex of hippocampus. And this had never been shown before.

So I don't take up research projects lightly in my lab. I had a stellar student coming and I thought, aha, this could be very interesting. We'll take a look.

Q. And who was that stellar student?

A. Joann Sweeney, now Joann Berger Sweeney, who's the Associate Dean at Wellsley College.

Q. That work you talked about with the nicotinic receptor that you did with Professor Whitehouse, was that published before January of 1986?

A. No. No. It was -- it was published later in '86.

Q. When Dr. Bonnie Davis approached you and asked you to carry out some animal tests on galanthamine, did you think that her proposal was simply a guess?

A. No. I mean, the -- her neuroendocrine signal was intriguing to me. There were a number of things that were intriguing. The neuroendocrine was intriguing.

And acetylcholine seemed to be intriguing, given what was going on with physostigmine and tacrine.
Q. Did her proposal seem to you scientifically well grounded?
A. The rationale was well grounded and -- and it fit in very nicely with the lesion model because that was the model where you could really see if there was a contribution of nicotinic receptors to -- you know, to the effects of acetylcholinesterase inhibitors.
Q. Did you think at the time it was obvious to use galanthamine as a treatment for Alzheimer's disease?
A. I wish I had thought of it.
Q. Do you tend to do obvious science in your lab?
A. No. And this became Joann Sweeney's thesis project, thesis projects at Hopkins. We have a committee that oversees them, that reviews them. If -- if somebody came in with an obvious research question, they would go back to the drawing boards and come up with something better, and their mentor would look rather silly. So this was not obvious.
Q. And I take it Dr. Berger Sweeney did, in fact, get her Ph.D. and move on in her career?
A. Yes. She has been -- she has been very successful.
Q. Let me --
A. Continues to collaborate with me.

on physostigmine and tacrine for treatment of Alzheimer's disease, and there was no treatment. Sounds good to me.

The second thing she said was it has this very unusual property of -- of acting at nicotinic receptors, enhancing nicotinic receptor function.

Number three, I had just -- I had just got done with a study with Peter Whitehouse for the first time showing there was striking reductions in nicotinic restrictors. The first time that was demonstrated as far as I know.

And that was in the face of normal muscarinic receptors.

So as I said, we don't do trivial experiments. We don't do obvious experiments. This seemed to me -- she had a proposal that connected the dots that raised very interesting questions and worth the effort to check it out in a model in which there is degeneration of cholinergic neurons in both nicotinic and muscarinic receptors would come into play.

Q. And the dots she connected, galanthamine, safe, humans will tolerate it, cholinesterase inhibitors; right?

A. Galanthamine in humans safe and well tolerated. Cholinesterase inhibitor, selective nicotinic effects,

and very modest muscarinic receptor side effects.
Q. Well, let's talk a little bit about the muscarinic and nicotinic receptors, but let me first ask you this: You, on your chart here, you have galanthamine as a weak inhibition of acetylcholinesterase; is that right?
A. I would say relatively -- it's relatively weak vis-a-vis physostigmine and tacrine.
Q. Now, this is under the term potency; right?
A. Yes.
Q. And you heard Dr. Domino yesterday say that when you have a weak inhibitor of acetylcholinesterase, you give a higher dose. That's it. It's got nothing to do with efficacy; isn't that right?
A. I answered that question before. I said there are two issues here. One is potency and one is efficacy and the lower the potency, the higher dose of an agent you have to give, and that raises the risk that that agent is going to interact with other things that cause side effects.

So generally, in drug development, one likes to go for increased potency to lower the risk of secondary adverse interactions.
Q. You know what the therapeutic window for galanthamine was? It was quite large, wasn't it?
A. On experimental animals it was maybe like

A. Yes, they would.
Q. Now let me ask you, generally, would a person of ordinary skill in the art in 1986 reading the patent be enabled to practice the claimed invention by administering galanthamine as a treatment for Alzheimer's disease?
A. Yes.
Q. Let me now turn you to what a person of ordinary skill in the art would understand from what the patent is saying. And let's start with the background.
MR. SIPES: If you could put the first paragraph under background up...
BY MR. SIPES:
Q. Do you see that first paragraph? There's a discussion of two Cozanitis articles?
A. Yes.
Q. And then there's a conclusion that these studies show an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine?
A. Yes.
Q. Would a person of ordinary skill in the art in 1986 know about the drug atropine?
A. Yes.
Q. What would he or she know about atropine?
A. It's a classic muscarinic cholinergic antagonist.

Blocks the effects at one of the two major receptors.
Q. Would a person of ordinary skill in the art in 1986 know that?
A. Yes.
Q. What would a person of ordinary skill in the art in 1986 understand about galanthamine from the first paragraph?
A. Well, they would understand -- several things. The first was that because ACTH is centrally regulated, and its release is -- is regulated by the brain and by -- through a cholinergic mechanism, that galanthamine had to be able to cross into the brain to release ACTH and cortisol.

- - -

A. (Continuing) The second thing is that the receptor type of two major receptors, the nicotinic and muscarinic receptors that galanthamine was acting upon was the nicotinic receptor because atropine was administered first. Atropine is a blocker in the blood and takes out the ACTH, the muscarinic receptors.

If you get release of the ACTH and release of the cortisol, you have to be acting at the nicotinic receptors in the central nervous system.

- - -

Q. And just so the record is clear, would a person of ordinary skill in the art in 1986 understand from the paragraph at Column 1, Line 11 to 21, therefore, that Dr. Davis was saying that galanthamine was enhancing central nicotinic cholinergic function?

A. Yes.

Q. Okay. Let me then turn to the second paragraph in Column 1, which is from Lines 22 to 25.

Do you see there's a description of -- let me try, Ilyuchenok and the appearance of --

MS. ULRICH: Your Honor, I'm sorry to interrupt, but I have an objection to this.

Nothing that Dr. Raskin just testified about with respect to the nicotinic receptors and what the art would teach was disclosed in his expert report, so we object. This is outside the scope and it's the first time that, frankly, we're hearing this.

MR. SIPES: Your Honor, we disagree. There's an extension section on enablement on the way in which a person of ordinary skill in the art would understand what the patent teaches.

THE COURT: Well, as I've always -- as I have come to deal with expert reports and testimony at trial, I will let it in. If an opposing party believes that it truly

is outside the scope of both the report and the deposition and that they were truly surprised, it will be brought up in post-trial, and the party proposing the testimony is at risk, obviously, for any retrial that might have to happen.

So you can certainly go forward, but I think that my standard has been clearly explained.

MR. SIPES: Thank you, your Honor.

BY MR. SIPES:

Q. Let me ask you, what would a person of ordinary skill in the art understand from the paragraph describing Ilyuchenok about galanthamine?

A. Well, this, as -- this is animal data in rabbits in, from which one can infer that peripherally administered into the vein, intravenous galanthamine, crosses the blood/brain barrier and affects brain waves.

Q. And let me then turn to the third paragraph. There's -- the third paragraph, which is Column 1, Lines 26 to 28, is a discussion of Krauz.

What would a person of ordinary skill in the art in 1986 understand from the discussion of Krauz?

A. That the -- that galanthamine, when, again, when administered to -- in an animal model, in this case, to a dog, increased short-term memory, which obviously is the cardinal symptom of Alzheimer's disease.

Q. And let me turn to the next paragraph in Column 1,

which is Lines 29 to 33, a discussion of the Chaplygina.

Do you see that?

What would a person of ordinary skill in the art understand about galanthamine in 1986 from that paragraph?

A. Yes. Well, let me break it into two parts.

Scopolamine, similar to atropine, is a drug, well-known drug that blocks the muscarinic acetylcholine receptor in the brain and will, when administered to animals, impair their ability to learn. So their amnesia is a reasonable word for that. This study was done in rats, and that -- and this was really the model we had for acetylcholine system disruption at the time, in terms of behavior, and the administration of galanthamine antagonized this effect or reversed the effects. So you give scopolamine, the rats can't remember. You give galanthamine and they can remember again.

Q. Now, let me turn your attention to the second column of the patent.

The second column proposes a model for describing Alzheimer's disease; is that correct?

A. Yes.

Q. Could you tell me where in the patent that is? Where a person of ordinary skill in 1986 would recognize the patent's description of a model for treating Alzheimer's

disease?
A. Right. So the -- are we talking about a model for the cholinergic deficit that --
Q. At Column 2, Line 45, to --
A. Right.
Q. -- to 57?
A. Right. So -- you want me to read that?
Q. Well, let me ask you.
A. Yes.
Q. There's a reference here to a model for Alzheimer's disease in humans by using an animal; is that correct?
A. Yes.
Q. And it refers to a selected lesion is placed on the subcortical nucleus.
A. Right.
Q. Resulting in cortical cholinergic deficiency.
A. Yes.
Q. What kind of cholinergic deficiency would result from the model for Alzheimer's disease set forth in the patent?
A. Well, this -- this would be an advance over the scopolamine model because this model does what we see in Alzheimer's disease. In Alzheimer's disease, it's the pre-synaptic acetylcholine neuron, the neuron that makes acetylcholine and then projects to the thinking parts of

the brain. That is damaged in Alzheimer's disease. And this model damages the site of origin of these pre-synaptic acetylcholine neurons, which are indicated in the nucleus basalis of Menert, and therefore, with damage to the pre-synaptic cholinergic neurons in this nucleus, you get an acetylcholine deficiency in the thinking parts of the brain, in the hippocampus and the -- and the neocortex.

And this really does, if you will, at least in part, mimic the cholinergic deficiency in Alzheimer's disease. Either gets at the basic, the basic lesion in -- at cholinergic system in Alzheimer's disease.

Q. Now, which part of the central cholinergic system does scopolamine block?

A. It blocks the post-synaptic system, the muscarinic receptor in the thinking part. So it ignores the whole other part that's damaged in Alzheimer's disease.

Q. And is the model that is set forth for Alzheimer's disease in the patent, is that limited to the muscarinic part?

A. No.

Q. What else does it include?

A. Well, it real really will affect all parts of -- all receptors for acetylcholine in the brain, because you're taking away acetylcholine, so all receptors will see less acetylcholine and will be stimulated less.

Q. Would it include the nicotinic receptor?
A. Yes.
Q. Would a person of ordinary skill in the art in 1986 recognize these differences between the model being proposed for Alzheimer's disease in the patent and the scopolamine model?
A. Yes.
Q. Would a person of ordinary skill in the art in 1986 recognize that the model for Alzheimer's disease set forth in the patent includes the nicotinic as well as the muscarinic function?
A. Yes.
Q. Let me draw your attention to the reference to numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Does this reference nicotinic and muscarinic function?
A. Yes.
Q. Would a person of ordinary skill in 1986 reading that recognize that?
A. Yes.
Q. And how does that description differ from the earlier scopolamine model?
A. Well, the scopolamine model is -- is just one-half, if you will, of the -- of the cholinergic system, and it is one that -- you know, doesn't mimic Alzheimer's disease,

but does show you what happens when there's not enough acetylcholine in the brain in terms of the functions of the muscarinic side of the cholinergic system.

Q. And then the next sentence says, drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease.

Do you see that?

A. That is a reasonable inference.

Q. Now, we have gone over earlier the evidence about galanthamine as presented in the patent.

Would any of that evidence bear on whether or not galanthamine would be expected to succeed in this model to a person of ordinary skill in the art in 1986?

A. Yes.

Q. Could you explain that?

A. The -- the earlier parts of the patent describe that galanthamine gets in the brain, it's a cholinesterase inhibitor.

So we know that it's going to increase the amount of acetylcholine in the synapse that both types of receptors see, but it -- it also -- the earlier part of the patent would assure that the nicotinic part of the cholinergic system would not be ignored by this drug, because this drug has been demonstrated to affect the cholinergic system and has to be at the nicotinic site when the muscarinics are

taken out of the picture by administering atropine.
Q. So would a person of ordinary skill in the art in 1986 reading the patent believe that the assertion in the patent that galanthamine is a treatment for Alzheimer's disease was supported by the evidence presented for the effects of galanthamine and the model for Alzheimer's disease presented?
A. Yes.
Q. I believe you heard defendants' experts suggest that Dr. Bonnie Davis' invention was just a guess. Did you hear, I think it was Dr. Levy said, if the Court rejected his obviousness testimony, then his testimony was that it was a guess. Do you recall that?
A. Yes.
Q. Do you believe a person of ordinary skill in the art in 1986, reading the patent and its description of galanthamine and its description of a model for Alzheimer's disease, would view the invention as just a guess?
A. No.
Q. What -- how would they see it?
A. Well, I tell you how I saw it as a person in the art. I certainly wouldn't have come up with this. I was impressed that Dr. Davis did.
I think that the way it looks to me is that what happens -- what happened here is what happens in science so

the Cozanitis articles in the patent in the context of the patent, in the context of all the other art assembled in the patent and the description of the animal model in the patent.

What would a person of ordinary skill in the art understand the inventor to be saying about galanthamine as described in the Cozanitis papers when it's assembled this way?

A. Well, it -- it's saying that in a reasonable model for Alzheimer's disease, cholinergic deficit, galanthamine would account for the nicotinic side of the cholinergic system.

Q. And would a person of ordinary skill in the art, seeing a model described that was a cholinergic deficiency model for Alzheimer's in a patent that also cited Cozanitis, would they be -- would they be inclined -- how would they read the Cozanitis results in light of its presentation of patent that sets forth the cholinergic model?

A. It suggests that it's a nicotinic receptor stimulating compound.

Q. And let me ask you, generally, would the reading, a person of ordinary skill in the art, a teaching that a person of ordinary skill in the art would take away from the evidence about galanthamine in the papers under

won't be addressing this motion until I address post-trial briefing. So it is not really a motion practice as far as I'm concerned and is a matter to be addressed in post-trial briefing.

MR. LOMBARDI: Okay. Then I will address it as asking you to disregard the testimony rather than seek a mistrial in that context, then.

THE COURT: Well, generally, what happens, at least, and this has actually never happened, but what I say might happen is that if I find a party has truly gone beyond the scope of an expert report and admitted material that was not subject to the light and the testing of discovery, and if that material is critical enough that it plays out, half the time it doesn't in post-trial briefing, that if there is a mistrial, the party who proposed or offered the testimony would be responsible for the costs of any retrial. That is what the standard is.

MR. LOMBARDI: Okay. Thank you, your Honor.

MR. SIPES: Your Honor, just because I feel that things have been done a little one-sided, it should be clear, of course, that we disagree with their position.

THE COURT: Obviously.

MR. PAPPAS: Your Honor, before we call our

EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-KAJ (Consolidated)

SECOND EXPERT REPORT OF DR. MURRAY A. RASKIND

I. INTRODUCTION

1. This report supplements my opening expert report of July 28, 2006. I have been asked to review the claims made by Dr. Edward Domino and Dr. Allan Levey that U.S. Patent No. 4,663,318 ("the '318 patent") is invalid due to anticipation, obviousness, or lack of enablement. This report sets forth my opinions concerning the validity of the '318 patent.

2. In forming the opinions described in this report, I have reviewed the reports of Dr. Domino and Dr. Levey, the documents discussed in those reports, the materials referenced in my opening report and in Attachment A to this report. I have also relied upon my more than 30 years experience as a clinician and researcher in Alzheimer's disease and knowledge of the relevant literature and state of the art in forming my opinion.

3. In summary, it is my opinion that the '318 patent is not invalid due to anticipation. The central reference relied upon by the defendants' experts -- P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71:45-47 (1974) (the "Bhasker article") -- does not in any way describe the use of galantamine for the treatment of Alzheimer's disease. In fact, no literature as of 1986 described or even suggested galantamine to treat Alzheimer's

disease. Furthermore, the Bhasker article would not have been accessible using standard reference search techniques of those skilled in the art.

4. It is also my opinion that the '318 patent is not invalid as obvious given the state of the art as of 1986. Neither the references relied upon by Dr. Levey and Dr. Domino nor any other publications in the field at that time suggest in any way the use of galantamine for the treatment of Alzheimer's disease.

5. It is further my opinion that Dr. Davis' '318 Patent would enable one of ordinary skill in the art to practice the claimed invention. The '318 patent outlines an approach for Alzheimer's disease researchers to confirm the efficacy and tolerability of the invention and describes the appropriate dose titration (beginning with a low dose and increasing the dose until a therapeutic response is noted or drug intolerance intervenes) to enable one skilled in the art to treat an Alzheimer's patient with galantamine.

II. A PERSON OF ORDINARY SKILL IN THE ART

6. A person of ordinary skill in the art in treating Alzheimer's disease in 1986 would have been a medical doctor treating elderly patients, that is, a physician likely to have responsibility for the care of patients suffering from Alzheimer's disease.

7. I disagree with Dr. Levey's and Dr. Domino's description of the level of ordinary skill in the art to the extent they assert a person of ordinary skill would be "a M.D. or Ph.D. interested in the field of Alzheimer's disease research" (Levey ¶ 19) actually engaged in Alzheimer's research. I believe their description exaggerates the level of skill of the ordinary person. In 1986, the majority of doctors treating Alzheimer's patients had been taught little about the disease in medical school, and very few had any training or experience in the field of

Alzheimer's research. Thus, the level of "ordinary" skill in the field of treating Alzheimer's patients would have come from being a doctor encountering and caring for patients with the disease.

8. However, the level of skill that was ordinary in 1986 does not affect my opinions concerning the validity the '318 patent. Even under the definition given by Dr. Domino and Dr. Levey of the person of ordinary skill in the art, it would remain my opinion that the '318 patent is not invalid for reasons of anticipation, obviousness, or lack of enablement.

III. ANTICIPATION

9. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). In order for that article to anticipate claims 1 and 4 of the '318 patent, I understand that this article must describe the invention claimed in those patent claims. That is, the article must describe, to one of ordinary skill in the art, each and every element of those claims.

10. I have been informed that the statutory requirement for anticipation of a patent also requires the invention to be patented or described "in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). For the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of

the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

11. Defendants' experts have asserted that the Bhasker article anticipated the '318 patent. They are incorrect. A person of ordinary skill would not interpret the Bhasker article in 1986 to suggest that Bhasker describes galantamine as a treatment for Alzheimer's disease.

12. Bhasker's only reference to galantamine is in a context clearly unrelated to Alzheimer's disease. Specifically, galantamine is discussed as a "deinhibitory" treatment for "local brain damage." (p. 46). Bhasker states that the Russian neuroscientist Dr. Luria and his colleagues "have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct [stroke] etc., by deinhibitory procedures and re-education of the rest of the brain." They go on to quote Dr. Luria as defining "deinhibition" as "facilitation of acetylcholine activity by small daily doses of cholinesterase inhibitors (Neostigmine, Gallanthamine etc.)." (p. 46).

13. Alzheimer's disease is not a type of local brain damage. It is not analogous to "tumour, head injury, or infarct." It is also noteworthy that this concept of "deinhibition" as described by Dr. Luria is not and never has been an approved or recognized treatment for local brain injury or any other neurologic disorder in Western medicine.

14. Alzheimer's disease is never mentioned by Bhasker. He does not even use the term "Senile Dementia" that prior to 1970 was often used (albeit incorrectly) to denote late onset Alzheimer's disease. Nonetheless, Dr. Levey and Dr. Domino assert that the Bhasker article's reference to "progressive dementia" would be understood to encompass Alzheimer's disease. (Levey ¶ 99; Domino ¶ 79). They assert that one of ordinary skill would understand that the Bhasker description of "irreversible cases belong[ing] to the category of dementias where there

is a progressive fall-out of neurons and the course of the illness is rapidly downhill" encompasses Alzheimer's disease. (p. 45). I disagree.

15. It is well known that the onset of Alzheimer's disease progresses gradually over an average 8-10 years and as long as 15 years. In fact, the early stage of Alzheimer's disease progresses so slowly that the emergence of the clinical picture is classically considered "insidious." The 1984 Merck Manual, cited by Dr. Domino (Domino ¶ 79) and Dr. Levey (Levey ¶ 99), states that "the most common clinical picture is of slow disintegration of personality and intellect." Berkow R, *Dementia. Merck Manual of Diagnosis and Therapy*, (14th ed. 1982), at 1305 (emphasis added). Additionally, Rathman and Conner, also cited by Dr. Levey (Levey ¶¶ 78, 102-103) and Dr. Domino (Domino ¶ 86), note "[t]he onset generally is insidious occurring over several years." Rathman and Conner, "Alzheimer's Disease, Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacy, 18: 684-691, 684 (1984). Thus, a person of ordinary skill would not view the course of an Alzheimer's patient as proceeding "rapidly downhill."

16. Nor does the Bhasker article suggest galantamine as a treatment for "progressive dementia." In fact, the article reaches the opposite conclusion. It expressly states that progressive dementias are untreatable. Bhasker concedes that "[w]ith regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (p. 45)(emphasis added). Management generally refers to environmental and behavioral approaches that reduce distress -- not treatment of the disease.

17. The fact that Bhasker lumps neostigmine with galantamine as an agent for "deinhibition" further indicates that Bhasker is not describing galantamine as a therapy for Alzheimer's disease. Neostigmine cannot penetrate the blood brain barrier and would not have

access to the brain following oral or even intravenous administration. Therefore, neostigmine would be a totally illogical treatment for a brain disease such as Alzheimer's disease.

18. The Bhasker article would not have taught a person of ordinary skill interested in either Alzheimer's disease or galantamine in 1986 because it was inaccessible using any standard search or index technique available at the time. Specifically, in 1986, the Index Medicus, which was the only widely used source of cited medical literature, did not contain articles appearing in the Indian journal The Antiseptic in which the Bhasker article was published.

IV. NON-OBVIOUSNESS

19. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I addressed objective considerations of non-obviousness in my opening report. In forming my opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention and also whether it would have provided such a person with a reasonable expectation of success in doing so.

20. Dr. Domino and Dr. Levey contend the '318 patent was obvious in light of the prior art, primarily relying upon select physostigmine clinical trials which they claim demonstrate that galantamine would have been obvious as an effective treatment for Alzheimer's disease. They are incorrect.

A. Prior Art - Physostigmine and Tacrine Clinical Trials

21. Physostigmine clinical trials did not "clearly show[] that the drug was effective in treating dementia symptoms associated with Alzheimer's disease" as Dr. Levey declares. (Levey ¶¶ 36, 113). In fact, physostigmine had not and still has not been demonstrated to be clinically effective. The results of the clinical studies on physostigmine as of 1986 were equivocal at best and their conclusions controversial in the field. Articles cited by Dr. Levey and Dr. Domino confirm this.

22. Mohs et al., "Oral Physostigmine Treatment of Patients with Alzheimer's Disease," Amer. J. Psychiatry, 142(1):28-33 (1985), cited by Dr. Levey (Levey ¶ 76), studied oral physostigmine in 12 Alzheimer's patients. The authors do not describe physostigmine as therapeutically effective. Instead, they conclude that the results could be interpreted from a clinical perspective either to demonstrate that "physostigmine, in the doses used in this study, does not have therapeutic benefits comparable to those seen with L-dopa in Parkinson's disease or with neuroleptics in schizophrenia" because it produced "a consistent and clinically evident improvement in symptoms for only about 30% of patients." (p. 31). The authors call for large clinical trials to identify individuals likely to benefit from oral physostigmine. (p. 32).

23. In "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," J Amer Geriatrics Soc., 33:749-57 (1985) cited by Dr. Levey (Levey ¶ 83) and Dr. Domino (Domino ¶ 41), Mohs et al. studied the acute effects of intravenous and oral physostigmine. They found that intravenous physostigmine modestly enhanced memory in most patients, but they were unable to correlate improvement with any "clinical variable." (p. 755). Oral physostigmine (the root of administration that would be necessary in clinical practice) slightly improved memory in roughly half of the patients. The authors acknowledge that "the search for any reasonably effective

pharmacologic treatment must address several different problems if it is to succeed" but warned about difficulties in diagnosis, the presence of neurochemical deficits other than acetylcholine in Alzheimer's patients, and the difficultly in determining whether a cholinomimetic drug is in fact improving a patient's cholinergic activity. (p. 755). However, the authors note that even when these conditions are met, "the use of such drugs could be severely limited" due to cholinergic cells having relatively few postsynaptic nonoverlapping projections. (p. 756)(emphasis added). Therefore, it would be difficult for surviving cholinergic cells to compensate functionally for lost cholinergic neurons by increasing their firing rate. Furthermore, none of these drugs (cholinesterase inhibitors) may be able to duplicate the phasic action of cholinergic cells in transmitting information.

24. K. Davis and Mohs, "Enhancement of Memory Processes in Alzheimer's Disease with Multiple-Dose Intravenous Physostigmine," Am. J. Psychiat., 139(11): 1421-24 (1982), similarly recognized the clinical limitations of their work. The authors administered physostigmine intravenously to Alzheimer's patients. While low doses of intravenous physostigmine transiently improved the ability of patients with Alzheimer's disease to store information into long-term memory, the authors caution that "until there is long-term administration of cholinomimetic agents to patients with Alzheimer's disease, it will be impossible to judge their ultimate clinical utility." (p. 1423)(emphasis added).

25. B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5):310-16 (1983), cited by Dr. Levey (Levey ¶ 32), acknowledge that the clinical utility of cholinomimetics like physostigmine had not been demonstrated. The authors reviewed pharmacologic enhancement of the cholinergic system in light of the insight learned from Parkinson's disease, a disease that reflects a deficiency of

dopamine. They declare that "positive effects of cholinomimetics have been reported; however, a level of clinical utility has not been achieved." (p. 313)(emphasis added). One explanation they offer in their attempt to account for the differential effect of dopamine and acetylcholine agonists is that "currently available cholinergic agents are unable to substantially influence symptoms of AD." (p. 313)(emphasis added).

26. In "Cholinergic Modulation of Memory in Rats, Psychopharmacology (Berlin), 87(3):266-71 (1983), cited by Dr. Levey (Levey ¶ 32), V. Haroutunian et al. reported that both the anticholinesterase agents including physostigmine and the post-synaptic cholinergic agonists agents arecoline and oxotremorine enhanced retention of learned responses in rats at low doses and impeded retention at high doses. The article notes that prior studies found the effects the drugs in this study to be conflicting "with some authors finding potentiation of learning and memory, others reporting disruption of memory processes, and still others finding no significant effects." (p. 269). The authors' sole reference to treatment of Alzheimer's disease is their speculation that "[i]f this generalization [about similar effects in man] should prove valid in experiments with normal human subjects, it may be possible to use these or similar cholinergic compounds in the treatment of memory disorders such as those characteristic of Alzheimer's disease." (p. 270). However, the article's suggestion that cholinergic agents may impede retention at higher doses would discourage its clinical use. None of the compounds is described as therapeutically effective in Alzheimer's patients.

27. C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2):185-97 (1983), cited by Dr. Domino (Domino ¶ 85), reviewed studies of the cholinesterase inhibitors physostigmine and tacrine in Alzheimer's patients. The authors note that the "only currently available relatively safe pharmacologic agents

of this type are physostigmine, which produces chronic enhancement of the cholinergic system by competitively inhibiting acetylcholinesterase, and tetrahydroaminoacridine (THA)[tacrine], a centrally-acting reversible acetylcholinesterase inhibitor with a longer half-life than physostigmine." (p. 189). They acknowledge that the variability of physostigmine test results, both in terms of overall efficacy and specific areas of improvement, has generated debate over the clinical utility of cholinesterase inhibitor therapies." (p. 189). Furthermore, they noted that the practical clinical utility of the drugs remains uncertain. (pp. 191-92).

28. Johns and her colleagues cast doubt on the efficacy of cholinesterase inhibitors like physostigmine and tacrine in treating Alzheimer's disease. They conclude that those drugs "share a fundamental limitation in that they are dependent on an intact presynaptic neuron to provide a substrate for their activity." (p. 192). Instead, the authors point to postsynaptic muscarinic agonist like oxotremorine as "a more ideal compound." (p. 192). Finally, the authors expressly reject Dr. Levey's and Dr. Domino's claim that clinical utility has been demonstrated for any cholinergic approach. They declare that "[t]he success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT [senile dementia of the Alzheimer's type] awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193).

29. The articles Dr. Levey and Dr. Domino rely on simply do not demonstrate that physostigmine or tacrine were therapeutically effective for the treatment of Alzheimer's disease as of 1986. Even the laundry list of articles cited in Dr. Levey's report (Levey ¶ 83), without explanation, demonstrate limited, inconclusive, and at times, negative results of physostigmine studies. Levy, et al., "Research Subject Recruitment for Gerontological Studies of

Pharmacological Agents," Neurobiology of Aging, 3(1): 77-79 (1982)(noting potential problems with recruitment, sample size, and diagnosis can raise issues with interpretation of Alzheimer's disease study results); Smith and Swash, "Physostigmine in Alzheimer's Disease," The Lancet, 1:42 (1979)(reporting that physostigmine appeared to improve name recall but none of the other memory tests); Peters, et al., "Effects of Physostigmine and Lecithin on Memory in Alzheimer's Disease," Annals of Neurology, 6(3): 219-21 (1979)(finding neither physostigmine nor lecithin alone consistently improved long-term memory processes and noting that physostigmine and lecithin had no obvious effect on general cognitive efficiency or social functioning during the brief course of the study); K. Davis, et al., "Physostigmine: Improvement of Long-Term Memory Process in Normal Humans," Science, 201(4352):272-74 (1978) (noting considerable variability between subjects in their physostigmine study).

30. In fact, many studies known to those skilled in the art failed to demonstrate any positive effect of physostigmine and tacrine on symptoms of Alzheimer's disease. Jotkowitz, "Lack of Clinical Efficacy of Chronic Oral Physostigmine in Alzheimer's Disease" Ann. Neurol., 14:690-691, 691 (1983)(finding "no improvement" from physostigmine and declaring "the present study confirms the previous report of the lack of benefit of physostigmine in AD and extends the observation to long-term oral administration.")(emphasis added); Kaye, et al., "Modest Facilitation of Memory in Dementia with Combined Lecithin and Anticholinesterase Treatment," Biol. Psychiatry, 17:275-90 (1982)(finding no overall effect of tacrine alone on cognitive function in patients with Alzheimer's disease); Drachman, et al. "Memory Decline in the Aged: Treatment with Lecithin and Physostigmine," Neurology, 32:944-50, 949 (1982)(declaring that "physostigmine failed to improve performance on memory tasks" in healthy elderly subjects selected because they were believed to show a decline in memory and

cognition and more sensitivity to cholinergic manipulation); Wettstein, et al., "No Effect from Double-Blind Trial of Physostigmine and Lecithin in Alzheimer's Disease," Ann Neuro 12:210-212, 211 (1983)(concluding "[n]o improvement in recent memory or other psychological functions could be demonstrated [with physostigmine]."); Sullivan, et al. "Physostigmine and Lecithin in Alzheimer's Disease," Aging, 19: 361-67, 362 (1982)(finding that "physostigmine infusion did not produce any reliable change in the performance of these patients as a unitary group."); Caltagirone, et al., "Oral Administration of Chronic Physostigmine Does Not Improve Cognitive or Mnestic Performances in Alzheimer's Presenile Dementia," Intern J. Neuroscience, 16:247-249, 248 (1982)(concluding "no difference was found for the results obtained on MDB[Mental Deterioration Battery] by AD patients before and after treatment [of physostigmine]."); Ashford, et al., "Physostigmine and its Effect on Six Patients," Am J Psychiatry, 138(6):829-30, 830 (1981) (finding that physostigmine "did not improve learning or memory … in older patients who were moderately to severely demented" and noting a "trend toward poorer verbal retention and less improvement on trials after patients had received physostigmine on the Buschke wordlist learning test" and "[a] similar trend toward poorer visual retention on the Benton visual retention test was noted after physostigmine."); Delwaide, et al., "Acute Effect of Drugs upon Memory of Patients with Senile Dementia," Acta Psychiat. Belg., 80:748-54 (1980)(finding physostigmine produces no improvement on memory but noting in contrast that the hormonal treatment lysine-vasopressin and the nootropic piracetam did improve memory).

31. Nor did those skilled in the art reviewing these clinical trials find that they stood for the proposition that "the ideal drug candidate for treating Alzheimer's disease would perform like physostigmine." (Levey ¶ 36). Raymond Bartus and his coauthors in 1986 reviewed the

physostigmine literature and found that "[a]lthough positive effects have been obtained in both aged humans and nonhuman primates with memory impairments, the effects are quite subtle and require strictly controlled test conditions and special attention to large individual variations in the most effective dose." Bartus et al., "Cholinergic Treatment for Age-Related Memory Disturbances: Dead or Barely Coming of Age?" in Crook, T., et al., eds., *Treatment Development Strategies for Alzheimer's Disease* 421-450 (1986), at 428. Nonetheless they found that "[w]hatever the positive results that have been claimed or obtained with cholinergic agents, one must recognize that they are extremely subtle, quite variable, and offer little or no significant therapeutic relief in activities of daily living." (p. 428)(emphasis added). In fact, the article declares that that "we are probably a long way from achieving an effective treatment for the symptomatic loss of cognitive function in senescent or demented patients." (p. 441). See also Bartus et al., "Cholinergic Hypothesis: Its History and Future," in Olton, et al., eds., *Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives* (Annals of the New York Academy of Sciences), 444:332-58 (May 30, 1985).

32. Bartus was not alone in his opinion. Kaye Rathmann and Christopher Conner, which Dr. Levey and Dr. Domino themselves cite, wrote in 1984 that "[d]espite encouraging results with physostigmine, the clinical importance and usefulness of this class of agents remain undetermined." K. Rathmann and C. Conner, "Alzheimer's Disease Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacy, 18:684-91, 689 (1984). The authors review a number of studies involving physostigmine and conclude: "[c]learly, controlled studies evaluating long-term treatment are required to determine the clinical usefulness of acetylcholinesterase inhibitors in Alzheimer's disease ...." (p. 688). Furthermore,

Dr. Berg, a pioneer neurologist in academic Alzheimer's disease research, noted in 1984 that "there have been inconsistencies in the findings from various laboratories in experiments testing the cholinergic hypothesis. Responses of patients with AD to cholinomimetic drugs and other agents to promote cholinergic transmitter function have been spotty and disappointing." Berg, "Aging and Dementia," in *Neurological Pathophysiology* 250-273 (1984), at 270.

33. Even when small and transient improvements occurred in one or a few cognitive tasks after single-dose physostigmine administration, such results were inadequate for inferring clinical efficacy. These acute, short term trials could not by the nature of their design demonstrate clinically efficacy. Any improvements found in such tests are not sufficient to constitute clinically meaningful improvements. Smaller improvements in cognitive test scores do not constitute effective therapy -- the therapy must result in clinical benefits.

34. The FDA emphasized this in its 1990 Guidelines for the Clinical Evaluation of Antidementia Drugs. Leber, "Guidelines for the Clinical Evaluation of Antidementia Drugs: First Draft" (Nov. 8, 1990). To be approved as a treatment for Alzheimer's disease, a drug must establish that it "has a clinically meaningful effect" and "exerts its effect on the 'core' manifestations of dementia"; that is, on a global assessment performed by a skilled clinician. (Guidelines at 4.4.2). The requirement of improvement on a global assessment scale precluded the approval of drug products that "produce no clinically meaningful effects on the overall status (e.g., health, function, etc.) of demented patients, but do because of their pharmacologic activity, cause the detectable changes in patient performance on objective tests that are of uncertain clinical relevance." (Guidelines at 4.4.2.). Clinical studies on physostigmine and tacrine as of 1986 did not even approach establishing the sort of reliable, clinically meaningful improvements in Alzheimer's patients that constitute a treatment.

35. The comments at the FDA's 1989 Antidementia Drug Assessment Symposium, approximately three years after Dr. Bonnie Davis' invention made this clear. As mentioned in my opening report, I was a participant of that symposium. There many of the leading clinical investigators in the field of Alzheimer's disease (including many of the authors whose works are cited by Dr. Domino and Dr. Levey) discussed and debated the challenges of finding a treatment for Alzheimer's disease, including the obstacles to obtaining reliable, clinically meaningful results addressing the global improvement of the disease.

36. Dr. Leber, Director of the FDA's Division of Neuropharmacological Drug Products, stated the purpose of the forum was for "open and free exchange of information and ideas among acknowledged experts about the development, testing, and assessment of drug products that might be classified as antidementia agents." (FDA Antidementia Drug Assessment Symposium Transcript 19:9-13). He recognized the very discouraging efforts to date to find an effective treatment of any sort for Alzheimer's disease. As he noted, "at this point in time, even a safe and effective symptomatic treatment for some cardinal sign and symptom of Alzheimer's would constitute a substantive therapeutic advance." (10:2-5). In trying to explain the lack of success in finding a useful treatment to help Alzheimer's patients in any way, Thal decried "the lack of an approved antidementia drug" as "a reflection of the inadequacies of the drugs so-far tested, not of our assessment methodologies or imagined regulatory biases." (17:23-25)(emphasis added).

37. Dr. Drachman explained that the lack of approval was not simply due to heightened FDA regulations. "Our biggest problem" in finding a effective drug, according to Drachman, is not "that we can't nail down, using precise measures, the exact degree of efficacy

of powerful and effective drugs" but that "[w]e don't have any drugs that are really doing a hell of a lot. That is where I would start." (37:25-38:4).

38. I, myself, expressed frustrations I had with attempting to find an effective treatment for Alzheimer's disease. I noted that a recent study at our Alzheimer's disease research center failed to demonstrate that an antidepressant was superior to placebo for depression complicating Alzheimer's disease. These results surprised me and my colleagues for we believed based on open label clinical experience that antidepressants indeed appeared effective for depression in Alzheimer's patients. Our study convinced me that "no matter what aspect of Alzheimer's disease you wish to treat, a controlled trial is absolutely necessary." (65:9-11). I warned that "if you base your judgment of efficacy on large clinical experience after several years, all of these drugs will be effective. Everybody believes, especially if they have a convincing care provider, that whatever is being given to them is working somehow, at least the care providers do. And I think that is dangerous." (65: 11-14).

39. Dr. Thal similarly recognized the limitations of the studies conducted to date. "I think everyone has agreed that to definitively release a drug, one needs a controlled trial." (67:19-20).

40. Results of open clinical studies in and of themselves would not necessarily provide a treatment for Alzheimer's disease. As Dr. Thal explained, mere changes to test scores are in and of themselves insufficient to demonstrate clinically therapeutic and meaningful results:

> it has to be a clinically-observable effect by someone and that if you increase the point score of a dementia patient on any cognitive test that you show, but that neither a clinician nor a family member nor another member of society can discern that effect on that individual, then it is not worth releasing that drug. (111:23 -112:3).

41. The sentiments and concerns expressed by those experts in the field at the Antidementia Symposium in 1989 make it clear that the state of the art had not provided any sort of reliable, clinically meaningful improvements in Alzheimer's patients that would support the conclusion that any treatment, let alone cholinesterase inhibitors like physostigmine and tacrine, were therapeutically effective as a treatment for Alzheimer's disease.

42. No article referenced by Dr. Levey and Dr. Domino point to any drug being clinically effective. As of January 1986, no drug had been demonstrated clinically effective as a treatment for Alzheimer's disease.

B. Motivation to Combine

43. In 1986, a person of ordinary skill in the art would not have found that galantamine was a treatment for Alzheimer's disease. They would not have been motivated to combine the literature about physostigmine and tacrine in Alzheimer's disease with the literature about galantamine use for other conditions.

44. None of the literature cited by Dr. Domino or Dr. Levey describes galantamine as a possible treatment for any dementia including Alzheimer's disease. In fact, some of the prior art argues against the use of galantamine for dementia. The Pernov article describes principal application of Nivaline [galantamine] as treatment for "diseases of the neuromuscular apparatus ... and disease of the peripheral motoric neurons." K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry and Neurology and Medical Psychology Bulletin on Research and Practice, 13(11) 416-420 (1961)(translation at Mylan(GAL) 05984, 05985). In Alzheimer's disease, central activity is required. Substantial peripheral effects would cast doubt on galantamine tolerability.

45. Nor would its possible use in reversing the central effects of scopolamine be persuasive. Dr. Levey and Dr. Domino rely on such articles by Baraka, et al., "Reversal of Central Anticholinergic Syndrome by Galanthamine," JAMA, 238:2293-2294 (1977) (Levey ¶¶ 77, 115; Domino ¶ 89), D.A. Cozanitis, "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anaetheist, 26, 649-650 (1977) (Levey ¶¶ 75, 103, 115-116), or D.A. Cozanitis, "L'hydrobromide de Galanthamine: Unsubstitute du Sulfate D'eserine (Physostigmine) pour le Traitement des Effects Cerebraux dex Substances Anti-Cholinergiques," Nouv. Presse Med., 7(45):4152 (1978)(Domino ¶ 88). This reliance is misplaced as none of those articles discusses Alzheimer's disease or dementia. Scopolamine induces a temporary delirium (reversible disruption of brain physiology) -- not a chronic and progressive dementia secondary to death of brain neurons. The fact that galantamine, like physostigmine and other cholinergic agents, had efficacy in reversing the central effects of scopolamine would not suggest to one of ordinary skill in the art that galantamine was a substitute for physostigmine in treating Alzheimer's patents.

46. In "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging, 17:225-230 (1981), cited by Dr. Domino (Domino ¶ 42), Mohs et al. criticize the scopolamine model as a guide to Alzheimer's research. The authors recognized that Alzheimer's disease does not involve a chemically-induced blockade of cholinergic receptors: "we know of no disease in which memory is impaired due to cholinergic blockade. Alzheimer's disease appears to affect primarily the presynaptic functions of cholinergic neurons and affects receptors only to a lesser extent." (p. 229).

47. Drs. Levey and Domino still claim that pharmacologic properties of galantamine made it an obvious substitute for physostigmine. In particular, they point to galantamine's

purported longer duration of action. However, in 1988, Dr. Domino himself claimed that "galanthamine is only as long acting as physostigmine but much less potent." Domino, E.F., "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., *Current Research in Alzheimer Therapy* 295-303 (1988) at 301(emphasis added). Any promising substitute for physostigmine in the treatment of Alzheimer's disease, where the results from physostigmine itself were, at best, small and inconsistent, would demand a more potent cholinesterase inhibitor.

48. One of ordinary skill in the art would not have been motivated to substitute galantamine for physostigmine in the treatment of Alzheimer's disease. Galantamine is chemically very different from physostigmine and tacrine with a different molecular structure which can have profound effects on pharmacologic properties and activity. Furthermore, galantamine is still a weak inhibitor of acetylcholinesterase. It is now appears that the efficacy of galantamine is due in part to its positive allosteric modulatory effect which appears to compensate for its weak cholinesterase inhibition.

49. Galantamine was also deemed by those skilled in the art as less potent than physostigmine or tacrine, making it a poor substitute for physostigmine or tacrine in treating Alzheimer's disease. The acetylcholinesterase inhibitory effect of galantamine was demonstrated 10-12 times less than that of physostigmine. Nesterenko L.N., "Effect of Galanthamine on the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakologia Toksikologia, 28(4): 413-414 (1965)(translation at SYN RAZ-0013374). Tacrine was known to be about approximately 100 times more potent as an acetylcholinesterase inhibitor than galantamine. Tonkopii, V.D. et al., "Interaction of reversible inhibitors with catalytic centers and allosteric sites of cholinesterases." Bull. Exp. Biol. Med., 86:400-401

(1976)(translation at SYN RAZ-0013159-62). The literature was clear to those skilled in the art. Paskov, D.S., "Galantamine," in *New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology*, Kharkevich D.A. (ed.) Springer Verlag (1986), at 654 ("The inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine and neostigmine."); D. Mihailova, et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods Fund. Exptl. Clin. Pharmacol., 11:595-601 (1985).

50. Those searching for a treatment for Alzheimer's disease in 1986 based on any perceived promise of physostigmine would certainly not seek a weaker cholinesterase inhibitor. The clinical studies on physostigmine, at most, taught that high levels of cholinesterase inhibition were necessary to achieve positive results in Alzheimer's patients: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had a smaller percent of cholinesterase inhibition." Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142:28-33, 32 (1985).

51. Nor would any increased duration of action have persuaded one skilled in the art to overlook galantamine's weaker cholinesterase inhibitor activity. As of January 1986, the understanding of the pharmacokinetics of galantamine was limited. The articles that did discuss its pharmacokinetics did not portray it as having a particularly long half-life. Bretagne, et al., for example, found that, at equivalently potent doses, "Galanthamine is faster in onset and more transient in duration than that of neostigmine" and reported that "[t]he Bulgarian authors who studied Galanthamine extensively showed that the action of this product persists over two

hours." Bretagne, et al., "Essis Cliniques en Anesthesiologie D'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (translation at JAN RAZ-00134056-57, 134061). Yet Mohs, et al., indicated that "steady-state levels" for oral physostigmine could be achieved with 2 hour dosing. Mohs, et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Pschiat. 142: 28-33 (1985). Other researchers noted that oral physostigmine had a "much longer" duration of action than previously suspected. Thal et al., "Oral Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Ann. Neurol. 13:491-96, 495 (1983) (observing that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected."). Hence, in January 1986, galantamine would not have appeared clearly longer acting than physostigmine.

52. As Dr. Domino recognized in 1988, from the perspective of treating Alzheimer's disease, galantamine is simply "only as long acting as physostigmine but much less potent." (p. 301) (emphasis added). Thus, far from appearing an equivalent but longer acting version of physostigmine, as Dr. Levey and Dr. Domino suggest, galantamine would have appeared to be precisely the reverse -- as a weaker but not necessarily longer acting version of that drug.

C. Reasonable Expectation of Success

53. To a person of ordinary skill in the art in January 1986, there would not have been a reasonable expectation of success in using galantamine to treat Alzheimer's disease. Physostigmine was not seen as clinically successful and galantamine was viewed only "as long acting as physostigmine but much less potent." Furthermore, there was considerable skepticism

at the time that any cholinesterase inhibitor strategy would prove clinically successful as a treatment for Alzheimer's disease as indicated in my first report.

V. ENABLEMENT

54. I understand that to be valid, a patent must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. §112. A patent is enabling even if some experimentation is required, as long as it is not unduly extensive.

55. Dr. Domino and Dr. Levey assert that the '318 patent does not meet the "enablement" requirement of patent law because "it would not inform one of ordinary skill in the art that galantamine would be a therapeutically effective treatment for Alzheimer's disease." (Levey ¶ 120). I disagree. The '318 patent states directly that galantamine is a therapeutically effective treatment for Alzheimer's disease. It outlines an approach for Alzheimer's disease researchers to confirm the efficacy and tolerability of the invention by providing the steps appropriate for confirming Dr. Bonnie Davis' insight concerning galantamine -- most significantly, the manner of carrying out animal testing to confirm the proposed efficacy. ('318 patent col. 2:45-57).

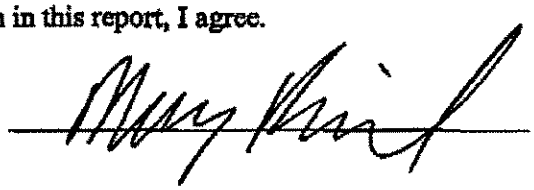
56. Dr. Levey and Dr. Domino also assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121). Again, I disagree. The patent describes the appropriate dose titration (beginning with a low dose and increasing the dose until a therapeutic response is noted or drug intolerance intervenes) to enable one skilled in the art to treat an Alzheimer's patient with galantamine.

('318 patent col. 1: 64-66). It is clear that a person of ordinary skill would be able, using standard clinical practice, to titrate doses for his or her patients so as to find a therapeutically effective dose within the claimed range.

57. Dr. Levey and Dr. Domino also suggest that Dr. Bonnie Davis did not provide the Patent Office with the necessary science in prosecuting the '318 patent. I disagree. While I am not an expert in patent prosecution and while I understand that such arguments have no relevance to anticipation, obviousness, and enablement of the '318 patent, I believe Dr. Bonnie Davis provided the Patent Office with scientifically fair and balanced information.

58. As I have already stated, The Antiseptic, let alone that particular Bhasker article, was not accessible using standard reference search techniques of those skilled in the art and would not, in any event, have been understood to relate to Alzheimer's disease at all. Additionally, she did discuss the cholinergic deficit associated with Alzheimer's disease in her patent -- in connection with describing an animal model that involved "a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease." ('318 patent, col. 2:48-50). And she directed the Patent Office to the scientific literature that discussed the cholinergic hypothesis and cholinesterase inhibition. Amendment Responsive to Office Action of April 10, 1986 (citing to Kendall, "Therapeutic Progress- Review XVIII Alzheimer's Disease," Journal of Clinical and Hospital Pharmacy, 10:327-36 (1985) and Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7):1125-30 (1986)). Furthermore, Dr. Davis stated in her submission to the Patent Office that physostigmine had demonstrated "useful results" despite its poor therapeutic index and the lack of any effective treatment. As set forth in this report, I agree.

Date: September 11, 2006



ATTACHMENT A

Documents

1. "FDA Antidementia Drug Assessment Symposium," Department of Health and Human Services, Public Health Service, Food Drug Administration, Peripheral and Central Nervous System Drugs Advisory Panel (June 15, 1989)(transcript).

2. United Kingdom Patent No. 942,200

3. United States Patent No. 4,663,318

4. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]

5. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]

6. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]

7. Shire complaint filed in Vienna Commercial Court [SYN RAZ 0018366 - 18374]]

8. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ 0000031-0000039]

9. Physician's Desk Reference (2006)

10. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

Publications

1. Ashford, et al., "Physostigmine and its Effect on Six Patients," American Journal of Psychiatry, 138(6): 829-830 (1981).

2. Baraka, A, et al., "Reversal of Central Anticholinergic Syndrome by Galanthamine," JAMA, 238(21): 2293-2294 (1977).

3. Bartus, et al., "The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions," in D. Olton, et al., eds., *Annals of the New York Academy of Sciences; Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives* 444:332-258 (1985).

4. Bartus, RT, et al., "The Cholinergic Hypothesis of Geriatric Memory Dysfunction," Science, 17: 408-417 (1982).

5. Bartus, RT, et al., "Cholinergic Treatment for Age-Related Memory Disturbances: Dead or Barely Coming of Age?" in Crook, T., *et al.*, eds., *Treatment Development Strategies for Alzheimer's Disease*, 421-450 (1986).

6. Berg, L., "Aging and Dementia," in *Neurological Pathophysiology* (1984).

7. Berkow, R, Ed., *Dementia. Merck Manual of Diagnosis and Therapy,* Fourteenth Edition, 1305-1309 (1982).

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10. Bonner T, et al., "Identification of a Family of Muscarinic Acetylcholine Receptor Genes," Science, 237:527-532 (1987).

11. Bretagne, M, et al., "Essais Cliniques en Anesthesiology d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1965). (translation at JAN RAZ-00134056-57)

12. Caltagirone, et al., "Oral Administration of Chronic Physostigmine Does Not Improve Cognitive or Mnestic Performances in Alzheimer's Presenile Dementia," Intern J. Neuroscience, 16: 247-249 (1982).

13. Coyle, JT et al., "Alzheimer's Disease: a Disorder of Cortical Cholinergic Innervation," Science, 219: 1184-1190 (1983).

14. Cozanitis, DA, et al., "A Comparative Study of Galanthamine Hydrobromide and Atropine/Neostigmine in Conscious Volunteers," Anaesthesist, 20: 41 6-421 (1971).

15. Cozanitis, DA, "Galanthamine Hydrobromide Versus Neostigmine. A Plasma Cortisol Study in Man," Anaesthesia, 29(2): 163-8 (1974).

16. Cozanitis, DA, "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anaesthesist, 26: 649-650 (1977).

17. Cozanitis, DA, "L'hydrobromide de Galanthamine: un Substitute du Sulfate d'eserine Physystogmine) pour le Traitement des Eflets Cerebraux des Substances Anti-cholinergiques," La Nouvelle Presse Medicale, 7: 4152 (1978).

18. Cozanitis, DA, et al., "The Effect of Galanthamine Hydrobromide on Plasma ACTH in Patients Undergoing Anaesthesia and Surgery," ACTA Anaesthesiol Scand., 24(3):166-8 (1980).

19. Daskalov, D, et al., "Nivalin: Application in Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes," MBI Medico-Biologic Information, 3: 9-11 (1980).

20. Davis, KL, et al., "Physostigmine: Improvement of Long-term Memory Processes in Normal Humans," Science, 201: 272-274 (1978).

21. Davis, KL, et al.. "Enhancement of Memory Processes in Alzheimer's Disease with Multiple-dose Intravenous Physostigmine," Am J Psychiat, 139: 1421-1424 (1982).

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EXHIBIT C

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